V. CLAIMS

What is claimed is:

1. A method of treating a disorder in a subject comprising administering to the subject a substance, wherein the substance modulates of nonsense-mediated mRNA decay in the pioneer round of translation.

2. The method of claim 1, wherein the disorder is an inherited genetic disorder.

3. The method of claim 2, wherein the genetic disorder can be selected from the group consisting of cystic fibrosis, hemophilia, mucopolysaccharidoses, muscular dystrophy, anemia, glycolytic enzyme deficiency, connective tissue disorder, DNA repair disorder, dementia, Sandhoff disease, epidermolysis bullosa simplex, insulin resistance, maple syrup urine disease, hereditary fructose intolerance, inherited immunodeficiency, inherited cancer, carbohydrate metabolism disorder, amino acid metabolism disorder, lipoprotein metabolism disorder, lipid metabolism disorder, lysomal enzymes disorder, steroid metabolism disorder, purine metabolism disorder, pyrimidine metabolism disorder, metal metabolism disorder, porphyrin metabolism disorder, and heme metabolism disorder.

4. The method of claim 1, wherein the disorder is an acquired disorder.

5. The method of claim 4, wherein the acquired disorder is a mutation in p53.

6. The method of claim 4, wherein the acquired disorder is a mutation in BRCA-1.

7. The method of claim 4, wherein the acquired disorder is a cancer.

8. The method of claim 7, wherein the cancer is selected from the group consisting of lymphoma, B cell lymphoma, T cell lymphoma, leukemia, carcinoma, sarcoma, glioma, blastoma, neuroblastoma, plasmacytoma, histiocytoma, melanoma, adenoma, mycosis fungoide, hypoxic tumor, myeloma, metastatic cancer, bladder cancer, brain cancer, nervous system cancer, head and neck cancer, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, liver cancer, colon cancer, cervical cancer, cervical carcinoma, breast cancer, epithelial cancer, renal cancer, genitourinary cancer, pulmonary cancer, esophageal carcinoma, hematopoietic cancers, testicular

cancer, colorectal cancer, and prostatic cancer.

9. The method of claim 1, wherein the subject is a mammal.

10. The method of claim 1, wherein the modulation is a decrease in nonsense-mediated mRNA decay.

11. The method of claim 1, wherein the modulation is an increase in nonsense-mediated mRNA decay.

12. The method of claim 1, wherein the substance interacts with Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, or Rrp41.

13. The method of claim 1, wherein the substance is a functional nucleic acid, siRNA, peptide, protein, antibody, or chemical.

14. A method of screening for a substance that modulates a nonsense-mediated mRNA decay (NMD) complex comprising

(a) incubating the substance with the complex, and

(b) assaying for a change in NMD, an increase or decrease in NMD activity indicating a modulating substance.

15. The method of claim 14, wherein the complex comprises Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

16. The method of claim 14, wherein the complex comprises one or more of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

17. The method of claim 14, wherein the complex comprises at least two members of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

18. The method of claim 14, wherein the complex comprises at least three members of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80,

hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

19. The method of claim 14, wherein the complex comprises at least four members of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

20. The method of claim 14, wherein the complex comprises at least five members of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

21. The method of claim 14, wherein the complex comprises at least six members of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

22. The method of claim 14, wherein the complex comprises at least seven members of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

23. The method of claim 14, wherein the complex comprises at least eight members of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

24. The method of claim 14, wherein the complex comprises at least nine members of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

25. The method of claim 14, wherein the complex comprises at least ten members of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

26. The method of claim 14, wherein the complex comprises at least eleven members of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

27. The method of claim 14, wherein the complex comprises at least twelve members of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

28. The method of claim 14, wherein the complex comprises at least thirteen members of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

29. The method of claim 14, wherein the complex comprises at least fourteen members of the group consisting of Upf2, Upf3, Upf3X, PABP2, CBP20, CBP80, hSmg5/7a, hSmg5/7b, hSmg5/7c, Dcp2, PM/Scl100, poly (A) ribonuclease (PARN), Rat1, Xrn1, and Rrp41.

30. A method of screening for a substance that modulates nonsense-mediated mRNA decay (NMD) comprising

(a) incubating the substance with a stably transfected cell comprising a reporter gene with a nonsense-mutation, and

(b) assaying the amount of NMD in the cell, wherein a increase or decrease in the amount of mRNA relative to the amount of mRNA in the absence of the substance indicates a substance that modulates NMD activity.

31. A method of screening for a substance that inhibits nonsense-mediated mRNA decay (NMD) comprising

(a) incubating the substance with Upf2 and Upf3 forming a substance-Upf2-Upf3 mixture, and

(b) assaying the amount of Upf2-Upf3 complex present in the mixture, wherein a decrease in the amount of Upf2-Upf3 complex relative to the amount of Upf2-Upf3

complex in the absence of the substance indicates that the substance inhibits NMD.

32. The method of claim 31, wherein the Upf2 has at least 80%, 85%, 90%, or 95% identity to the sequence set forth in ATCC No. AF318574, or fragment thereof.

33. The method of claim 31, wherein the Upf3 has at least 80%, 85%, 90%, or 95% identity to the sequence set forth in ATCC No.AF318575, or fragment thereof.

34. A method of screening for a substance that inhibits nonsense-mediated mRNA decay (NMD) comprising

(a) incubating the substance with Upf2 and Upf3X forming a substance-Upf2-Upf3X mixture, and

(b) assaying the amount of Upf2-Upf3X complex present in the mixture, wherein a decrease in the amount of Upf2-Upf3X complex relative to the amount of Upf2-Upf3X complex in the absence of the substance indicates that the substance inhibits NMD.

35. The method of claim 34, wherein the Upf2 has at least 80%, 85%, 90%, or 95% identity to the sequence set forth in ATCC No.:AF318574 or a fragment thereof.

36. The method of claim 34, wherein the Upf3X has at least 80%, 85%, 90%, or 95% identity to the sequence set forth in ATCC No.:AF318576 or a fragment thereof.

37. A method of screening for a substance that modulates nonsense-mediated mRNA decay (NMD) comprising,

a) administering a substance to a system, wherein the system comprises the components essential for NMD activity, and

b) assaying the effect of the substance on the amount of NMD activity in the system, wherein a substance which causes a change in the amount of NMD activity present in the system compared to the amount of NMD activity in the system in the absence of composition is a modulator.

38. A method of modulating nonsense-mediated mRNA decay (NMD) activity comprising administering a substance, wherein the substance is identified by the method of claim 37.

39. A method of making a substance capable of modulating nonsense-mediated mRNA decay (NMD) activity comprising admixing a substance identified by the method of claim 29 with a pharmaceutically acceptable carrier.

40. A substance made by the method of claim 39.

41. A method of making a modulator of nonsense-mediated mRNA decay (NMD) comprising,

a) administering a substance to a system, wherein the system comprises NMD activity,

b) assaying the effect of the substance on the amount of NMD activity in the system,

c) selecting a substance which causes a change in the amount of NMD activity present in the system compared to the amount of NMD activity in the system in the absence of substance, and

d) synthesizing the substance.

42. A substance that modulates NMD in the pioneer round of translation.

43. The substance of claim 42, wherein the substance is an antibody that modulates NMD.

44. The substance of claim 43, wherein the antibody binds Upf2.

45. The substance of claim 43, wherein the antibody binds Upf3.

46. The substance of claim 43, wherein the antibody binds Upf3X.

47. The substance of claim 43, wherein the antibody binds PABP2.

48. The substance of claim 43, wherein the antibody binds PARN.

49. The substance of claim 43, wherein the antibody binds Dcp2.

50. The substance of claim 43, wherein the antibody binds PM/Scl100.

51. The substance of claim 43, wherein the antibody binds Rat1.

52. The substance of claim 43, wherein the antibody binds Xrn1.

53. The substance of claim 43, wherein the antibody binds Rrp41.

54. The substance of claim 43, wherein the antibody binds hSmg5/7a.

55. The substance of claim 43, wherein the antibody binds hSmg5/7b.

56. The substance of claim 43, wherein the antibody binds hSmg5/7c.

57. The substance of claim 42, wherein the substance is a vector comprising a nucleic acid that encodes a protein that modulates NMD.

58. A vector comprising a nucleic acid that encodes a protein that modulates NMD.

59. A cell comprising the vector of claim 57.

60. The substance of claim 42, wherein the substance is siRNA that modulates NMD.

61. The substance of claim 60, wherein the siRNA binds Upf2.

62. The substance of claim 60, wherein the siRNA binds Upf3.

63. The substance of claim 60, wherein the siRNA binds Upf3X.

64. The substance of claim 60, wherein the siRNA binds PABP2.

65. The substance of claim 60, wherein the siRNA binds PARN.

66. The substance of claim 60, wherein the siRNA binds Dcp2.

67. The substance of claim 60, wherein the siRNA binds PM/Scl100.

68. The substance of claim 60, wherein the siRNA binds Rat1.

69. The substance of claim 60, wherein the siRNA binds Xrn1.

70. The substance of claim 60, wherein the siRNA binds Rrp41.

71. The substance of claim 60, wherein the siRNA binds hSMg5/7a.

72. The substance of claim 60, wherein the siRNA binds hSmg5/7b.

73. The substance of claim 60, wherein the siRNA binds hSmg5/7c.